IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Richard S. BEIN, et al.

Title: COMPOSITIONS FOR USE IN EMBOLIZING BLOOD VESSELS COMPRISING HIGH LEVELS OF CONTRAST AGENT

Appl. No.: 10/796,604

Filing Date: March 8, 2004

Examiner: Jagadishwar R. SAMALA

Art Unit: 1618

DECLARATION OF BRIAN M. STRAUSS UNDER 37 C.F.R. §1.132

I, Brian M. Strauss, hereby declare that:

1. I, Brian M. Strauss, earned a BSME in Mechanical Engineering from University of California, Santa Barbara in 1986 and MBA from California State University, Long Beach in 2000.

2. I have been an employee of ev3 Neurovascular and its predecessor company, Micro Therapeutics Inc., since July 1996. During this period, I have worked extensively with embolic compositions to treat vascular diseases for over 5 years, including monitoring clinical studies relating to commercial development of Onyx® embolic composition, comprising ethylene vinyl alcohol copolymer ("EVOH"), dimethyl sulfoxide ("DMSO"), and tantalum.

3. I have reviewed the subject U.S. Patent Application Serial Number 10/796,604 (hereinafter, the "Bein Application") and the U.S. Patent Examiner's remarks regarding the use of a specific ratio of biocompatible polymer to contrast agent to be used for the embolization of blood vessels in the Office Action mailed on September 14, 2007. As set forth in detail below,

compositions for embolizing vascular sites using a high amount of contrast agent with the correct ratio of polymer to contrast agent provide superior and unpredictable advantages, such as improved visualization while maintaining a cohesive precipitate, over preexisting embolic compositions.

4. The Bein Application recites, *inter alia*, an embolic composition having a high amount of contrast agent (i.e., greater than about 40% to about 60%) to improve visualization of the composition. The compositions of the invention exhibit improved visualization during delivery compared to composition which have lower amounts of contrast agent. The compositions of the invention also require that the ratio of biocompatible polymer to contrast agent be greater than 0.055 to maintain a cohesive polymer precipitate. The cohesiveness is important because if the polymeric precipitate mass is not cohesive, fragments and particles from the mass will be shed and washed downstream with the blood.

5. It is my opinion that by providing greater than about 40% to about 60% contrast agent and a ratio of biocompatible polymer to water-insoluble biocompatible contrast agent of greater than 0.055, the resultant combination provides a polymer precipitate that is relatively cohesive, and also provides a high level of visualization (i.e., radiopacity) during delivery. The visualization is enhanced because the composition appears more radiopaque and is easier to see during delivery through, for example, fluoroscopy. Improved visualization is a desired property for an embolic composition because the practitioner is able to provide a more effective and more accurate fill of the vasculature malformation. Without a good visualization of the embolic composition, the practitioner may be at risk for not providing a complete fill or an overfill of the vascular malformation. The present invention composition overcomes the limitations of the prior art by providing a composition that has a ratio of biocompatible polymer to water-insoluble biocompatible contrast agent of greater than 0.055 in combination with a percentage of biocompatible contrast agent that from about 40% to about 60%.

6. In addition to the aforementioned results, additional experiments were performed which describe a prior art composition, "Onyx HD 500" ("Onyx"), and other compositions

within the scope of the claimed invention, "Onyx HD 500 2.5x Ta." ("Onyx 2.5"). The procedure for visualizing the different samples is the same as described in Example 2 of the Specification. The procedure for measuring particulate generation (i.e., the cohesiveness) of the different samples is the same as described in Example 3 of the Specification. The biocompatible polymer used is ethylene vinyl alcohol copolymer (EVOH), the contrast agent is tantalum, and the solvent is DMSO. The table below provides the components of the additional compositions made and tested and also provides the cohesiveness test results.

Sample #	EVOH (g)	DMSO (g)	Tantalum (g)	% EVOH	% DMSO	% Tantalum	Ratio (EVOH to Tantalum)	Particles ≥10 μm per mL solution	Particles ≥25 μm per mL solution
Onyx	0.2	1.1	0.33	12.3	67.5	20.2	0.61	14.9	1.7
Onyx 2.5 #1	0.2	1.0	0.83	9.8	49.3	40.9	0.24	1.1	0
Onyx 2.5 #2	0.2	1.0	0.83	9.8	49.3	40.9	0.24	0.6	0
Onyx 2.5 #3	0.2	1.0	0.83	9.8	49.3	40.9	0.24	1.3	0.5

7. The visualization of the Onyx versus Onyx 2.5 samples is included in Fig. A. The Onyx 2.5 samples clearly provide darker lines compared to the Onyx samples which signifies that visualization is improved.

8. On the basis of our studies, it is my opinion that the present invention composition provides superior visualization while maintaining polymer cohesion over the compositions of the prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Irvine, CA, this 14 day of Feb, 2008.

Brian Strauss

Figure A